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Docket No. 9491e013-US-PC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF: CAMELLIA W. ADAMS, ET AL. GAU: 1647
SERIAL NO: 09/138,091 EXAMINER: SPECTOR, L.
FILING DATE: AUGUST 21, 1998
FOR: AGONIST ANTIBODIES

#29
B.G.J
9/5/02

APPEAL BRIEF

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Sir:

This is an Appeal under 37 C.F.R. §1.192 from the Final Rejection of the Primary Examiner dated October 23, 2001. Each of the topics required under Rule 192 is presented herewith and is labeled appropriately.

I. REAL PARTY IN INTEREST

The real party in interest in this patent application is:

Genentech Inc.
1 DNA Way
South San Francisco, California 94080-4990

II. RELATED APPEALS AND INTERFERENCES

The Applicants know of no related appeals or interferences that will directly affect, will be directly affected, or have any bearing on the Board's decision in this Appeal.

III. STATUS OF CLAIMS

Claims 46-57 are pending in the present application. Claims 1-45 have been canceled. No claims are allowed. Claim 49 is rejected under 35 U.S.C. §112, first paragraph and is considered by the Examiner to include an improper Markush group. Claims 46-48 and 50-57 are objected to for encompassing non-elected species in what is considered by the Examiner as an improper Markush group. Claims 46-57 are subject to an election of species requirement.

IV. STATUS OF AMENDMENTS

An Amendment filed under 37 C.F.R. §1.116 on February 25, 2002 has been entered.

V. SUMMARY OF THE INVENTION

The invention as defined by Claim 49 relates to an isolated nucleic acid encoding an agonist antibody, fragment or variant thereof which binds to human c-mpl. The agonist antibody, fragment, or variant thereof is selected from the group consisting of 12E10 (SEQ ID NO:79), 12B5 (SEQ ID NO:77), 10F6 (SEQ ID NO:74) and 12D5 (SEQ ID NO:78). The specific sequences of the antibodies listed in the Markush group of the claim are clearly defined within the application.

The invention as defined by Claim 50 relates to an isolated nucleic acid encoding an agonist antibody, fragment or variant thereof which binds to human c-mpl. The antibody, fragment or variant thereof is selected from the group consisting of: Ab1, Ab2, Ab3, Ab4, Ab5 and Ab6, wherein each Ab1-Ab6 includes a VH and VL chain, each VH and VL chain including CDR amino acid sequences designated CDR1, CDR2 and CDR3 separated by framework amino acid sequences, the amino acid sequence of each CDR in each VH and VL chain of Ab1-Ab6 is

selected from the table provided in the claim and specifically described in the application.

Claims 46, 47, 48, 51, 52, 53, 54, 55, 56, and 57 depend from Claim 50 and are partially defined by the same Markush group of Claim 50.

VI. ISSUES

The issues presented for consideration in this Appeal are:

Issue 1:

The Examiner erred in maintaining the rejection of Claim 49 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connects, to make and/or use the invention because of the alleged failure of the Applicants' statement of deposit for the claimed biological materials to comply with the requirements under 37 C.F.R. §1.806.

Issue 2:

The Examiner erred in contending that Claim 49 contains an improper Markush group and, for that stated reason, did not fully examine Claim 49 as required.

Issue 3:

The Examiner erred in contending that Claims 50-57 and 46-48 contain an improper Markush group and, for that stated reason, did not fully examine the claims as required.

VII. GROUPING OF CLAIMS

Group I, Claim 49.

Group II, Claims 50-57 and 46-48. The claims of Group II stand or fall together on the limited issue of this Appeal.

VIII. **ARGUMENT**

Background:

By amendment to the application on May 23, 2001, Applicants submitted new independent Claims 49 and 50 for consideration.

In the Office Action dated July 13, 2001, the Examiner imposed an Election of Species requirement for Claim 49 and Claim 50. Responsive to the Election of Species requirement, Applicants elected with traverse species AB5/12D5 on August 6, 2001.

The Examiner subsequently examined the elected species in the claims and determined in an Office Action dated October 23, 2001, that Claims 46-48 and 50-57 would be allowable if amended to delete non-elected species from the claims. The Examiner also determined that Claim 49 would be allowable if the deposit requirement was satisfied and non-elected species were deleted from the claim.

An Examiner's Interview with Applicants' representative was conducted on January 14, 2002, to discuss the remaining issues in the application. The issue of whether there were generic claims in the application was discussed. The Examiner's Interview Summary Record indicates there were no generic claims allowable and that the independent claims were Markush claims. The record indicates that no agreement was reached during the interview.

Applicants, by an Amendment dated February 25, 2002, amended the application to include the statement in the specification that a viable culture of the deposit would be maintained for at least 30 years and at least 5 years after the most recent request for the furnishing of a sample of the deposit was received by the depository from the date of the deposit. This statement specifically addressed the concerns of the Examiner as stated at page 3 of the Office Action dated

October 23, 2001. At that time, Applicants argued that according to MPEP §803.02, the Examiner is compelled to consider each of the non-elected species of the Markush group in turn.

In an Advisory Action dated March 5, 2002, the Examiner failed to withdraw the rejection of Claim 49 under 35 U.S.C. §112, first paragraph. The Examiner stated that the elected species is allowable over the prior art. The Examiner argued that the independent claims contained an improper Markush group, and accordingly the Examiner would not continue examination of non-elected species.

Issue 1: The Examiner erred in maintaining the rejection of Claim 49 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connects, to make and/or use the invention because of the alleged failure of the Applicants' statement of deposit for the claimed biological materials to comply with the requirements under 37 C.F.R. §1.806.

DROP (forgot)

Responsive to the rejection under 35 U.S.C. §112, first paragraph in the Official Action October 23, 2001, Applicants submitted an amendment on February 25, 2002, to the specification which included a deposit statement in full compliance with the requirements under 37 C.F.R. §1.806. The Advisory Action dated March 5, 2002 indicated that the Amendment would be entered; however, the Examiner did not withdraw the rejection of Claim 49 under 35 U.S.C. §112, first paragraph. The Applicants assert that the stated basis for the Examiner's rejection under 35 U.S.C. §112, first paragraph has been overcome by the Amendment dated February 25, 2002, which includes the appropriate required deposit statement, and the rejection of Claim 49 should therefore be withdrawn. The Advisory Action did not acknowledge that the Amendment complied with the Examiner's suggestion to submit the appropriate deposit statement and also

failed to indicate that the rejection of Claim 49 under 35 U.S.C. §112, first paragraph had been withdrawn. Applicants respectfully request that the Board reverse the Examiner's rejection of Claim 49 under 35 U.S.C. §112, first paragraph.

Issue 2: The Examiner erred in contending that Claim 49 contains an improper Markush group and, for that stated reason, did not fully examine Claim 49 as required.

The Examiner erroneously contends that Claim 49 contains an improper Markush group and on that basis has refused to fully examine Claim 49, as required under MPEP §803.02 and relevant case law. The Examiner's position in refusing to fully examine the species listed in the Markush group of Claim 49 is not in compliance with guidelines of the U.S. Patent and Trademark Office and is incorrect as a matter of law.

The U.S. Patent Office provides clear guidance for the examination of Markush claims:

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the group can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. (See MPEP 803.02)

The U.S. Patent and Trademark Office provides additional guidance for the Examiner when it is determined that the Markush-type claim includes members which are independent and distinct inventions.

> A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. §103 with respect to the other members(s). In applications containing claims of that nature, the examiner may require a provisional election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. ... should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. (Emphasis added)

In the present case, the species in the Markush group are few in number and, as antibodies which bind to human c-mpl, are closely related. The Examiner has determined that the elected species in the Markush-type claim is neither anticipated or obvious over the prior art. Under the guidelines of the U.S. Patent and Trademark Office, the remaining species of the claim should be fully examined. This the Examiner has refused to do.

The Office Action dated July 13, 2001, required an election of species for initial examination of the Markush claims. In a Response dated August 6, 2001, Applicants made the required election, albeit with traverse. In the Advisory Action, Paper Number 27, dated March 5, 2002, the Examiner indicated " the elected species is determined to be "allowable over the prior art." The MPEP, at §803.02 specifically states that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended." The Examiner, having found the elected species to be allowable over the prior art, has refused to comply with the published Patent Office guidance for the examination of applications. Instead, in the Advisory Action has taken the position that the claims include an improper Markush group. This position is inconsistent with the statement in the Examiner Interview Summary Record dated January 24, 2002 that the claim is a "Markush claim."

In refusing to fully examine the claims of the application, the Examiner has argued that, "With respect to the burden on the Examiner under the election of species requirement that was made, it is noted that there remains no generic claim. There is no provision for examination of additional species where there is no generic claim found allowable." By making this argument, the Examiner has confused the requirement for a "provisional election of a single species" in a Markush-type claim (MPEP §803.02) with a restriction requirement under 35 U.S.C. §1.121.

This type of confusion has been clearly addressed by the Federal Circuit. The Federal

Circuit has determined that, "An applicant is given, by the statute, the right to claim his invention with the limitations he regards necessary to circumscribe that invention, with the proviso that the application comply with the requirements of §112." (In re Weber, 580 F.2D 455, 458; 198 USPQ 328 (CCPA 1978)) The Court has also determined that, "As a general proposition, an applicant has a right to have each claim examined on the merits." (*Id.*) While acknowledging that a proper restriction requirement would not affect the right of the applicant eventually to have each of the claims examined in the form the applicant considers to best define his invention, the Court also made it clear that, if "...a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim." (*Id.*) Thus, the Court has recognized the negative effect on the applicants rights to have his claim examined on the merits when that single claim is divided and examined piece-meal. In the present case, the division of a single claim into separate and distinct claims would deprive the Applicants of their right to claim the invention as they choose and to have the claim fully examined on the merits.

The Examiner's concern over the burden of examining non-elected species fails to consider the Court-recognized priority of the applicant's statutory rights over the convenience of the Examiner. The Court has

> ...recognized that the PTO must have some means for controlling such administrative matters as examiner caseloads and the amount of searching done per filing fee. But, in drawing priorities between the Commissioner as administrator and the applicant as beneficiary of his statutory rights, we conclude that the statutory rights are paramount." (*Id.*)

Further, the Examiner has asserted that the Markush group of the present claims is improper because it lacks unity of invention. In making this assertion, the Examiner cites MPEP §803.02 as requiring that, "... unity of invention exists where compounds included within a

Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility." (See Advisory Action dated March 5, 2002). The Examiner does not argue that members of the Markush group in the present application share a common utility but does dispute that the Markush group members share a substantial structural feature. The Federal Circuit, in reversing the Board's determination that the application at issue in In re Harnisch contained an improper Markush group pointed out that all members of the Markush group were dyes and all had a single structural similarity. (In re Harnisch, 631 F.2d 716, 722; 206, USPQ 300 (CCPA 1980)). In that same case, the court restated the proposition that, "...in determining the propriety of a Markush grouping the compounds must be considered as wholes and not broken down into elements or other components." (*Id.*, citing In re Jones, 34 CCPA 1150, 162 F.2D 479, 74 USPQ 149 (CCPA 1947)). The Court also reaffirmed that such cases are to be determined on a "case-by-case basis." (*Id.*) Finally, the Court made it clear that the concept of unity of invention was not to be confused with "misjoinder under 35 USC §121 but instead that reference to the widely-recognized concept of unity of invention was made in order to suggest an appropriate term to apply where unrelated inventions are involved; that is inventions which are truly independent and distinct." (*Id.*)

In the present case, the Examiner does not dispute that the Markush group of the present claims share a common utility. The common utility of the members of the present Markush group is clearly stated in the claims as encoding an agonist antibody, fragment or variant thereof which binds to human c-mpl. With regard to the second requirement for unity of invention, that of a "single structural similarity" (Harnisch at 722), the Examiner has ignored the common structural similarity of antibodies which bind to human c-mpl, and without which the antibodies would not so bind.

Contrary to the Examiner's characterization of the Applicants' claims, the species of the Markush group of the Applicants' claims do in fact contain at least one "single structural similarity" in accordance with the unity of invention requirement described by the Court in Harnisch. Each of the species of the Markush group of the claims is an antibody that binds to human c-mpl and is distinctly defined by the sequences identified in the claims. The Examiner has ignored the U.S. Patent and Trademark Office published guidelines, which recognize the common structural features of antibodies applicable in this case. The U.S. Patent and Trademark website provides the following published guidelines related to general knowledge of the common structural characteristics of antibodies:

Example 16: Antibodies

> **Specification:** ... The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA and IgE. Antibodies contain an effector protein which is the constant region and a variable region that contains the antigen binding sites in the form of complementaritity determining regions and the framework regions. The sequence of constant regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. ... This is a mature technology where the level of skill is high and advanced.

See U.S. Patent and Trademark Office Written Description Guidelines: Example 16, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines").

As indicated above, the U.S. Patent and Trademark Office publicly recognizes the well defined structural characteristics of antibody binding, and the fact that the antibody technology is well developed and mature. Applicants' claims clearly indicate that a common structural characteristic of each of the species claimed by the Applicants is the portion of the antibody which binds to human c-mpl. It is equally clear that the binding portion of the antibody is essential to the utility of the claimed invention. It is therefore asserted that the Examiner's

characterization of the claims as lacking unity of invention and being an improper Markush Group is in error.

Further, on July 15, 2002, the Federal Circuit, in deciding the issue of the sufficiency of the written description in an application, wherein the description involved functional characteristics, referred to and relied on the same U.S. Patent and Trademark Office Guidelines cited above. To make clear its position, the Federal Circuit used a hypothetical example drawn from the U.S. Patent and Trademark Office Guidelines. The Court recognized that the Patent Office would find that the application complied with 35 U.S.C. §112, first paragraph for:

> a claim to an "isolated antibody capable of binding to X," not withstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm (Application of Guidelines"). ... We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement.

See Enzo Biochem, Inc. v. Gen-Probe Incorporated 2002 U.S. App. LEXIS 14328 (CAFC 2002).

The well-known common structural features of antibodies are thus recited by the U.S. Patent and Trademark Office in published guidelines. Those same guidelines have recently been discussed and relied upon by the Federal Circuit as providing an adequate written description of an invention. Applicants' specification and claims not only provide a functional description, which would be found adequate by the Federal Circuit under Enzo, but also provide the specific sequence list references for the claimed invention. The Markush group of the claims include a common utility and a common structural similarity necessary to the utility of the invention.

Issue 3: The Examiner erred in contending that Claims 50-57 and 46-48 contain an improper

Markush group and, for that stated reason, did not fully examine the claims as required.

Those arguments presented above to rebut the Examiner's assertion that Claim 49 includes an improper Markush group apply equally to the Examiner's equally erroneous assertion that Claims 46, 47, 48, 51, 52, 53, 54, 55, 56 and 57 also include an improper Markush Group. The invention of Claims 46, 47, 48, 51, 52, 53, 54, 55, 56 and 57 are clearly defined to include a Markush Group, the species of which share a common utility and have a common structural portion that is necessary to that common utility. Under the U.S. Patent and Trademark guidelines and the recognition of the validity of those guidelines by the Federal Circuit, it is clear that the Markush group of Claims 46, 47, 48, 51, 52, 53, 54, 55, 56 and 57 is proper and should be fully examined as required.

IX. CONCLUSION

The outstanding rejection of Claim 49 and the Examiner's objections to all claims of the application should be reversed for the reasons discussed above. Applicants respectfully request that this Board reverse the rejection of Claim 49 and further determine that the Markush group of Claim 49 and Claims 46, 47, 48, 51, 52, 53, 54, 55, 56 and 57 are proper Markush groups and are therefore subject to extended examination of the non-elected species as required under MPEP §803.02 and relevant case law.

Respectfully submitted,

PIPER RUDNICK LLP

Aug 26, 2002
Date

Steven B. Kelber
Registration No: 30,073
Attorney of Record

Perry E. Van Over
Registration No: 42,197

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No.: (202) 861-3900
Facsimile No.: (202) 223-2085

APPENDIX

Claims on Appeal

49. An isolated nucleic acid encoding an agonist antibody, fragment or variant thereof which binds to human c-mpl, wherein said agonist antibody, fragment, or variant thereof is selected from the group consisting of 12E10 (SEQ ID NO:79), 12B5 (SEQ ID NO:77), 10F6 (SEQ ID NO:74) and 12D5 (SEQ ID NO:78).

50. An isolated nucleic acid encoding an agonist antibody, fragment or variant thereof which binds to human c-mpl, wherein said antibody, fragment or variant thereof is selected from the group consisting of: Ab1, Ab2, Ab3, Ab4, Ab5 and Ab6, wherein each Ab1-Ab6 comprises a VH and VL chain, each VH and VL chain comprising CDR amino acid sequences designated CDR1, CDR2 and CDR3 separated by framework amino acid sequences, the amino acid sequence of each CDR in each VH and VL chain of Ab1-Ab6 is selected according to the following table:

Ab1:	**VH^{CDR1}**	**VH^{CDR2}**	**VH^{CDR3}**
	(SEQ ID NO: 1)	(SEQ ID NO: 3)	(SEQ ID NO: 5)
	(SEQ ID NO: 2)	(SEQ ID NO: 4)	(SEQ ID NO: 6)
	VL^{CDR1}	**VL^{CDR2}**	**VL^{CDR3}**
	(SEQ ID NO: 7)	(SEQ ID NO: 9)	(SEQ ID NO: 11)
	(SEQ ID NO: 8)	(SEQ ID NO: 10)	(SEQ ID NO: 12)
Ab2:	**VH^{CDR1}**	**VH^{CDR2}**	**VH^{CDR3}**
	(SEQ ID NO: 13)	(SEQ ID NO: 15)	(SEQ ID NO: 17)
	(SEQ ID NO: 14)	(SEQ ID NO: 16)	(SEQ ID NO: 18)
	VL^{CDR1}	**VL^{CDR2}**	**VL^{CDR3}**

	(SEQ ID NO: 19)	(SEQ ID NO: 21)	(SEQ ID NO: 23)
	(SEQ ID NO: 20)	(SEQ ID NO: 22)	(SEQ ID NO: 24)
Ab3:	**VH^{CDR1}**	**VH^{CDR2}**	**VH^{CDR3}**
	(SEQ ID NO: 25)	(SEQ ID NO: 27)	(SEQ ID NO: 29)
	(SEQ ID NO: 26)	(SEQ ID NO: 28)	(SEQ ID NO: 30)
	VL^{CDR1}	**VL^{CDR2}**	**VL^{CDR3}**
	(SEQ ID NO: 19)	(SEQ ID NO: 21)	(SEQ ID NO: 23)
	(SEQ ID NO: 20)	(SEQ ID NO: 22)	(SEQ ID NO: 24)
Ab4:	**VH^{CDR1}**	**VH^{CDR2}**	**VH^{CDR3}**
	(SEQ ID NO: 25)	(SEQ ID NO: 31)	(SEQ ID NO: 33)
	(SEQ ID NO: 26)	(SEQ ID NO: 32)	(SEQ ID NO: 34)
	VL^{CDR1}	**VL^{CDR2}**	**VL^{CDR3}**
	(SEQ ID NO: 35)	(SEQ ID NO: 21)	(SEQ ID NO: 23)
	(SEQ ID NO: 20)	(SEQ ID NO: 22)	(SEQ ID NO: 24)
Ab5:	**VH^{CDR1}**	**VH^{CDR2}**	**VH^{CDR3}**
	(SEQ ID NO: 36)	(SEQ ID NO: 38)	(SEQ ID NO: 40)
	(SEQ ID NO: 37)	(SEQ ID NO: 39)	(SEQ ID NO: 41)
	VL^{CDR1}	**VL^{CDR2}**	**VL^{CDR3}**
	(SEQ ID NO: 19)	(SEQ ID NO: 21)	(SEQ ID NO: 23)
	(SEQ ID NO: 20)	(SEQ ID NO: 22)	(SEQ ID NO: 24)
Ab6:	**VH^{CDR1}**	**VH^{CDR2}**	**VH^{CDR3}**
	(SEQ ID NO: 42)	(SEQ ID NO: 44)	(SEQ ID NO: 46)
	(SEQ ID NO: 43)	(SEQ ID NO: 45)	(SEQ ID NO: 47)
	VL^{CDR1}	**VL^{CDR2}**	**VL^{CDR3}**
	(SEQ ID NO: 48)	(SEQ ID NO: 50)	(SEQ ID NO: 52)
	(SEQ ID NO: 49)	(SEQ ID NO: 51)	(SEQ ID NO: 53).

51. The isolated nucleic acid of Claim 50, wherein said agonist antibody, fragment, or variant thereof is a humanized antibody, fragment or variant thereof.

52. The isolated nucleic acid of Claim 50, wherein said agonist antibody, fragment, or variant thereof is a non-naturally occurring antibody, fragment or variant thereof.

53. The isolated nucleic acid of Claim 50, wherein said agonist antibody, fragment, or variant thereof is a human antibody, fragment or variant thereof.

54. The isolated nucleic acid of Claim 50, wherein said agonist antibody stimulates proliferation, differentiation or growth of megakaryocytes.

55. The isolated nucleic acid of Claim 50, wherein said agonist antibody stimulates megakaryocytes to produce platelets.

56. The antibody of Claim 50, wherein said agonist antibody is selected from the group consisting of svFv, Fab, $F(ab')_2$ and IgG.

57. The antibody of Claim 50, wherein said agonist antibody is a monoclonal antibody.